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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

APPLICANT(S):	EDA *et al.*	EXAMINER :	G. Gabel	
SERIAL NO. :	09/827,846	ART UNIT :	1641	
FILED :	April 6, 2001			
FOR :	MICROPARTICLE ENHANCED LIGHT SCATTERING AGGLUTINATION ASSAY AND MICROPARTICLE REAGENTS THEREFOR			

Assistant Commissioner for Patents
Washington, D.C. 20231
Attention: Board of Patent Appeals and Interferences

BRIEF OF APPELLANT

This brief is in furtherance of the Notice of Appeal filed in this case on November 4, 2002. This is an appeal from the final Rejection of the Examiner dated June 4, 2002 rejecting Claims 1-17 and 19-21 and the Advisory Action of September 18, 2002. This Brief is submitted in triplicate and is accompanied by the requisite fees set forth in Section 1.17 of the Regulations.

REAL PARTY IN INTEREST

The real and only party in interest in this application is assignee of record Roche Diagnostics Corporation, Indianapolis, Indiana.

RELATED APPEALS AND INTERFERENCES

None.

STATUS OF CLAIMS

For purposes of Appeal, the status of the claims is (or will be) as follows:

Claims 1-17 and 20 are (or will be) rejected

Claims 18, 19 and 21 are (or will be) cancelled.

The appealed claims are: 1-17 and 20

STATUS OF AMENDMENTS

Claims 1-17 and 19-21 were finally rejected in the Office Action of June 4, 2002. Appellants' Request for Reconsideration filed September 3, 2002 presenting amended claim 1 and canceling claims 19 and 21 has been or will be entered for purposes of appeal according to the Advisory Action dated September 18, 2002. The Examiner indicated that claims 1-17 and 19-21 would be rejected. While no specific explanation was provided indicating how the amended claims would be rejected, the Examiner provided a general statement indicating that the request for reconsideration was considered but did "NOT place the case in condition for allowance because: the amendment of claim 1 fails to obviate the teaching and/or suggestion of the prior art of record" and because "the amendment of claim 1 raises new issues under 35 USC 112, second paragraph." (Advisory Action, 9/18/02)

SUMMARY OF THE INVENTION

The present invention provides a reagent for performing a microparticle enhanced light scattering agglutination assay that offers a larger dynamic range than heretofore known. (Specification, page 2, lines 18-21). The assay of the invention can be used for determining an analyte for which there are binding partners apt to be bound to microparticles that specifically recognize the analyte. (Id., page 10, lines 3-6). The assay reagent comprises a binary mixture of two particle types: 1) microparticles of strong light scattering properties carrying at least one binding partner of high reactivity (high affinity) for the analyte, and 2) particles of weak light scattering properties carrying at least one binding partner of low reactivity (low affinity) for the analyte (Id., page 6 lines 20-22 and page 7 lines 1-2).

The size and/or the refractive index ratio of the microparticles is such that they can cause light scattering at the wavelength used for detection of agglutinated microparticles. That detection wavelength is usually from 300 nm to 1200 nm. Accordingly, particle size is generally chosen to be substantially smaller or slightly smaller than that wavelength. The mean diameter of microparticles is suitably from 30 to 600 nm, preferably from 50 to 500 nm. (Id., page 8, lines 3-9). The particles of strong light scattering properties have preferably a higher refractive index and/or a larger size than the particles of weak light scattering properties. (Id., page 8, lines 7-9).

The binding partners (e.g. antibodies) of high and low affinity are selected so as to cause an agglutination reaction that is detectable by, for example, turbidimetry or nephelometry (Id., e.g., page 1, lines 8-17; page 4, lines 11-16; page 17, line 17). By using a binary mixture of two particle type populations, the measurements obtained from the high reactivity particles provide high precision in the low concentration range and the measurements of low reactivity particles provide an increase in binding at high concentrations even after the high affinity particles have

been saturated, avoiding the well known "hook effect." The assay shows an unexpectedly high dynamic range (DR) (Id., page 7, lines 2-3) for an agglutination assay.

Thus, the reagent of the invention comprises a mixture of microparticles of 30 to 600 nm (preferably from 50 to 500 nm) in diameter, including particles of strong light scattering properties carrying at least one binding partner of high reactivity (affinity) for the analyte and particles of weak light scattering properties carrying at least one binding partner of low reactivity (affinity) for the analyte. (Id., page 19, lines 2-5).

According to one preferred embodiment, the "particles of strong light scattering properties" and the "particles of weak light scattering properties" are microparticles of the same size but made of different materials, the material of the former particles having a substantially higher refractive index than the material of the latter particles. The ratio of the refractive index of the particles of strong light scattering properties to that of the particles of weak light scattering properties is then suitably at least 1.2, preferably at least 1.5. (Id., page 8, lines 10-16).

According to another preferred embodiment the "particles of strong light scattering properties" and the "particles of weak light scattering properties" are microparticles of the same material but having different sizes, the size of the former particles, referred to as "large particles", being substantially larger than that of the latter, referred to as "small particles". The mean diameter of the large particles is suitably from 160 to 600 nm, preferably from 190 to 500 nm. The ratio between the mean diameter of the large particles and the mean diameter of the small particles is suitably from 1.5 to 4.0, preferably from 1.7 to 3.2. (Id., page 8, lines 17-22 and page 9, lines 1-3).

ISSUES

Are Claims 1-8 and 10-12 unpatentable under 35 U.S.C. §103(a) over Grange *et al.* in view of Lindmo *et al.?* Is Claim 9 unpatentable under 35 U.S.C. §103(a) over Grange *et al.* in view of Lindmo *et al.*, further in view of Sutton *et al.*? Are Claims 13-17 and 20 unpatentable under 35 U.S.C. §103(a) over Grange *et al.* in view of Lindmo *et al.* further in view of Harchali *et al.* Is it proper to reconstruct the claimed microparticle agglutination reagent by substituting the individually distinguishable microparticles of Lindmo's flow cytometry reagents for the indistinguishable microparticles of Grange's agglutination reagents, assuming equivalencies which are not disclosed, in order to reject the claimed reagent although none of the references teaches differential characterization between microparticles in agglutination reagents? Is claim 1 unpatentable under 35 USC 112, second paragraph?

GROUPING OF CLAIMS

The claims stand or fall together.

ARGUMENT

The rejection of Claims 1-17 and 20 under 35 U.S.C. § 103(a) as being unpatentable over the teachings of Grange *et al.* (Journal of Immunological Methods, 18: 365-375 (1977)) in view of the teachings of Lindmo *et al.* (Journal of Immunological Methods, 126: 183-189 (1990)) only or further combined with either Harchali *et al.* (Clin. Chem. 40(3): 442-447 (1994)), or U.S. Patent 5,330, 891 awarded to Sutton *et al.* are improper.

Initially, the Examiner has admitted that Grange *et al.* fail to teach differential characterization of particles from specific size populations, differential reactivity and different dissociation constants between a pair of immunological binding partners as taught in the present

invention. The Examiner asserts that Lindmo *et al.* supplies the teaching that is lacking in Grange *et al.*.

In spite of the admitted shortcomings of Grange *et al*, the Examiner has asserted that one of ordinary skill in the art would have been motivated to incorporate the teachings of Lindmo *et al.* to arrive at the present invention agglutination reagent containing a binary mixture of particle types. The Examiner believes that Lindmo *et al.* teach that his method of using a pair of particles with high and low reactivity in an assay of one antigen by flow cytometry can easily be combined with the concept of using a mixture of distinguishable particles coated with antibodies of different specificities (or the same specificity but different reactivity towards differing epitopes) in a simultaneous (or homogenous) assay of antigens such as those taught by Grange *et al.*

Appellants assert that there is no such teaching in Lindmo *et al.*, and that the secondary reference, in fact, teaches away from assays such as those taught by Grange *et al.* since Lindmo *et al.* specifically calls for individually distinguishable microparticles. As in the present invention, the microparticles of Grange *et al.* are of a type and size that enhance "molecular size" of an analyte via *agglutination.* Thus, it is Appellants disclosure that provides a reagent with differential particle size, reactivity and dissociation constants between two immunological binding partners covalently bound or adsorbed thereon that dramatically improves the dynamic range in nephelometric and turbidometric agglutination assays.

Lindmo *et al.* teach an assay based on flow cytometry, wherein there is no aggregation of microparticles, and the amount of soluble labeled antibody is determined for each particle individually as they are separated and discriminated by a flow cytometer. A calibration curve for each particle with a distinguishing feature is generated. In stark contrast, Appellants' invention

teaches, *inter alia*, an assay based on microparticle-enhanced light scattering agglutination in which the measuring is done based on the whole aggregation of the binding partners bound to the microparticles and analyte. There is no necessity for and no possibility of determining the individual contributions of each particle or discriminating between particles having distinguishing features. Therefore, only one calibration curve has to be generated as opposed to multiple calibration curves for an assay by flow cytometry.

Thus, due to the great disparity between Appellants' Invention and the teachings of these references, it is respectfully submitted that one of ordinary skill in the art would ***never*** be motivated to combine the teachings of these references as the Examiner has done in making this rejection. Rather, ***Appellants' disclosure*** has provided motivation for the Examiner's attempt to combine these references. One of ordinary skill in the art would not be motivated to combine the references except by the application of hindsight based on the present claims. Absent a teaching or suggestion in the record that would motivate one of ordinary skill in the art to combine the references, they are not properly combinable.

The rejection of Claim 9 under 35 U.S.C. §103(a) as being unpatentable over Grange *et al.* in view of Lindmo *et al.*, further in view of Sutton *et al.* is improper. Based only on the fact that Sutton *et al.* teaches the use of oligonucleotide capture probes for a nucleic acid analyte, which is known in the art, it is respectfully submitted that one of ordinary skill in the art would not be led to create the reagent of Claim 9 by combining the teachings of Sutton *et al.* with Grange *et al.* and certainly not by combining the teachings of Sutton *et al.* with Lindmo *et al.*.

The rejection of Claims 13-17 and 20 under 35 U.S.C. §103(a) as being unpatentable over Grange *et al.* in view of Lindmo *et al.*, further in view of Harchali *et al* is improper. Harchali *et al.* teach a microparticle-enhanced nephelometric immunoassay for autoantibodies

with defined epitopic specificity based on the ability of these autoantibodies to inhibit agglutination. The instant Invention, however, utilizes an agglutination assay such as taught in Grange *et al.* and does not inhibit agglutination as in Harchali *et al.* It is respectfully submitted that one of ordinary skill in the art would not be led to create the reagent of Claims 13-17 and 20 by combining the teachings of Harchali *et al.* with Grange *et al.* or Lindmo *et al.*

THE REJECTIONS UNDER 35 U.S.C. 103 (a) ARE IMPROPER BECAUSE THERE IS NO TEACHING OR SUGGESTION TO COMBINE THE REFERENCES

MPEP 706.02(j) states that in order for the claims of the instant Application to be obvious in light of the teachings of the cited references:

> ...three basic criteria must be met.
>
> First, there must be some suggestion or motivation, either in the [reference itself], or in the knowledge generally available to one of ordinary skill in the art, to modify the reference....
>
> Second, there must be a reasonable expectation of success.
>
> Finally, the prior art reference (or references combined) must teach or suggest all the claimed limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art. (MPEP 706.02(j)).

A. THERE IS NO MOTIVATION TO MODIFY GRANGE *ET AL.*

Grange *et al.* fails render to render the Claims under appeal unpatentable because it neither teaches nor suggests differential characterization between microparticles of specific size populations, differential reactivity and dissociation constants between two immunological binding partners. Since the teachings of Grange *et al.* fail to suggest the diagnostic methodology

of Appellants' invention, it is respectfully submitted that no motivation can be drawn therefrom for one of ordinary skill in the art to prepare the reagents as claimed in Claims 1-17 and 20. Since the assay taught by Lindmo *et al.* does not involve agglutination, there would be no teaching therein from which one of ordinary skill in the art would be motivated to create such particles. Hence, it is respectfully submitted that the teachings of Grange *et al.* are not properly combinable with Lindmo *et al.*

Particle enhanced laser nephelometry and turbidimetry techniques require reagents containing relatively small particles (<1 μm in diameter) that enhance the "molecular size" of the incorporated analytes by specific aggregation. In both techniques, detection is performed at a wavelength, which lies fairly close to the particle sizes. Lindmo *et al* teaches a flow cytometry assay, that requires an assay reagent with particles of a relatively large size (7-10 μm in diameter) that can be individually distinguished in a flow cytometer.

Accordingly, Appellants maintain there is no motivation for one of ordinary skill in the art to substitute Lindmo's microparticles which are in the 7-10 μm diameter range with antibody adsorbed on their surfaces for the 300 nm particles with antibody covalently bound to their surfaces disclosed by Grange *et al.* because there is no reasonable expectation of success. Thus, it is respectfully submitted that the Examiner has impermissibly utilized hindsight in an unsuccessful attempt to reconstruct Appellants' invention from this combination of references. The Examiner cannot rely on hindsight to arrive at a determination of obviousness. *In re Fritch*, 23 U.S.P.Q.2d 1780, 1784 (Fed. Cir. 1992). The Court of Appeals for the Federal Circuit has stated that "selective hindsight is no more applicable to the design of experiments than it is to the combination of prior art teachings. There must be a reason or suggestion in the art for selecting the procedure used, ***other than the knowledge learned from the Appellants' disclosure***

(emphasis added)." [*Interconnect Planning Corporation v. Fed.*, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985)]. *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988).

B. THERE IS NO BASIS TO COMBINE THE REFERENCES TO RECONSTRUCT THE CLAIMED MICROPARTICLE AGGLUTINATION REAGENT BY SUBSTITUTING INGREDIENTS ASSUMING EQUIVALENCIES WHICH ARE NOT DISCLOSED

The Examiner admits that "there would have been no motivation to combine the microparticles taught by Grange with that of Lindmo for use as reagent in a method of microparticle enhanced agglutination assay" (Office Action of June 4, 2002, page 8). However, she attempts to reconstruct the claimed reagent of the present invention by improperly substituting a reagent ingredient from one reference for a reagent ingredient of the other reference assuming equivalencies that are not taught and do not exist. In supporting the obviousness rejection, The Examiner argues:

> "Lindmo *et al* specifically teach the two populations of microparticles as distinctly having 7 μm and 10 μm in diameter. Both microparticle types are coated with binding partners (antibody) having the same specificity but different reactivity" ... [T]he teaching of structural requirements of the microparticles taught by Grange is in itself combinable with the teaching of structural requirements of microparticles taught by Lindmo." Id.

Appellants submit that a reagent and its properties cannot be separated for purposes of making a rejection when the properties thereof are inherent and when a property, specifically the utility of the reagent, is the fundamental distinction that would not suggest combining the teachings of the two citations to arrive at claimed invention.

To support of her position, the Examiner relies on Masham 2 USPQ 2d 1647 (1987) for the proposition that:

" an intended use must result in a structural difference between the claimed invention and the prior art. If the prior art structure is capable of performing the intended use, it meets the claim." (See Office Action of June 4, 2002, page 9).

The Examiner assumes that substituting Lindmo's microparticles for Grange's microparticles would result in the claimed microparticle reagent. This reasoning entails equating "relatively large" (See Lindmo page 184, col. 2, lines 4-7) monodisperse antibody-coated microparticles with relatively small (300 nm range - See Grange, page 367, line 11) aggregating antibody-bound microparticles to reconstruct a hypothetical reagent. To make the substitution relied upon by the Examiner, the art must teach such equivalence. In point of fact not one of cited references teaches or suggests the equivalence of individually distinguishable mondisperse particles such as taught by Lindmo *et al.* are equivalent to particles used in a particle enhanced agglutination reagent system. Appellants emphasize that the issue is motivation to combine teachings from references directed to different purpose and assert that the Masham decision is inappropriate.

The test for obviousness is not whether the features of one reference may be bodily incorporated into another reference but whether one of ordinary skill in the art would turn to such references and would have a motivation to combine their teachings in a manner which renders the claimed subject matter obvious. The Federal Circuit has held that the mere fact that references can be combined does not cause the resulting combination to be obvious absent the prior art suggesting the combination. ACS Hospitals Inc. v. Montefiore Hospital, 732 F2d 1572, 221 USPQ 929,933 (Fed. Cir. 1984). In making such a combination, "there must be some reason for the combination other than the hindsight gleaned from the invention itself." Interconnect Planning Corp. v. Feil, 774, F2d 1132, 227 USPQ 543, 551 (Fed Cir. 1985).

Grange *et a.l*, in fact, teaches non-equivalence of agglutinated particles vs. monodisperse particles. Grange *et al.* observed that the intensity of light diffused by a suspension of monomers showed a linear relationship with the concentration of latex particles (Grange page 369, last full paragraph). On the other hand when the same measurements were performed on immunologically aggregated particles at constant antigen concentrations, the intensity of light diffused by increasing concentrations of latex particles was no longer linear. (Grange page 374, last paragraph). Appellants maintain that Lindmo's teachings directed to mondisperse particles are not necessarily predictive of the behavior of aggregated particles.

C. THERE IS NO MOTIVATION IN THE REFERENCES RELIED UPON THEMSELVES TO COMBINE THE TEACHINGS OF GRANGE *ET AL* AND LINDOMO *ET AL*. IN A MANNER WHICH RENDERS THE CLAIMED SUBJECT MATTER OBVIOUS BECAUSE THEY TEACH AWAY FROM ONE ANOTHER

Grange discloses the use of a specific particle type in agglutination assay applications but, by the Examiner's own admission, Grange *et al.* differs from the present invention in "failing to teach differential characterization between two microparticle populations. Grange *et al* also fails to teach differential reactivity and dissociation constants between two immunological binding partners" (See Office Action of June 4, 2002 Action, Page 4, lines 6-8). Lindmo *et al.* discloses differential characterization between two microparticle populations, differential reactivity and dissociation constants between two immunological binding partners in flow cytometry applications but does teach or suggest agglutination applications. Rather, Lindmo and Grange teach away from one anther in that Lindmo requires a reagent wherein relatively large particles remain monodispersed so that they can be individually detected by a flow cytometer and Grange requires a reagent wherein relatively small microparticles aggregate

to enhance the size and thus the light scattering properties of the immunological complexes into ranges detectable by nephelometry.

The Examiner's argument that it would have been obvious to have provided the reagents of Grange with the binary particle system of Lindmo *et al* is without merit. Appellants emphasize that Lindmo's particles are in a "relatively large" size range that do not posses the properties of the colloidal sized particles taught by Grange. The size, reagent solution and surface properties of Lindmo's particles render them individually distinguishable themselves (not as aggregates). Grange *et al.* makes no suggestion that the 7-10 μm particle sizes taught in Lindmo could be substituted for the 300 nm particles taught therein.

Moreover, Grange is directed to the overcoming the deficiencies in particles that contain adsorbed antibodies such as those taught by Lindmo *et al.* (See Lindmo, page 184, bottom of col. 2). Appellants maintain that one of ordinary skill in the art would not turn to the Lindmo reference in the first place for materials that might possibly be substituted for the particles disclosed by Grange *et al* .because the primary reference *teaches away* from particles with antibody or antigen adsorbed to their surface such as those taught in Lindmo. According to Grange *et al.*:

> "preparations of latex spheres containing *adsorbed* antigens or antibodies are difficult to standardize due to their tendency to autoagglutinate with changes in the pH and ionic force of the medium. These difficulties could be overcome with the use of latex particles having antigens or antibodies covalently bound to their surface in such a way that their immunological activity remains intact.....We now describe the use of antibody *bound* latex spheres to detect trace quantities of antigen by nephelometric assays" (Grange *et al.* page 365 and 366, emphasis added).

Thus, in the 300 nm diameter range appropriate for the agglutination assays taught by Grange *et al.* (which 20-30 is times smaller in diameter than that required for individual particle detection in a flow cytometer), the primary reference teaches away from Lindmo *et al.*

Since the assay of Lindmo *et al.* is based on principles unrelated to those for which the claimed reagent is suitable, there would be absolutely no suggestion therein for one or ordinary skill in the art to prepare a reagent possessing light scattering capabilities at wavelengths suitable for the detection of agglutinated microparticles. The amendment to claim 1 presented in Appellants' Request for Reconsideration and entered for purposes of appeal recites that the microparticles possess a property clearly outside of the scope and teachings of Lindmo *et al.* .

Turning to the specific teachings of Lindmo, Appellants maintain that Lindmo teaches away from use of reagents in which particles cannot be individually differentiated. " Thus, one pair of particles could be used to provide a binary assay for each antigen *with the additional requirement that all particle types in the assay be individually distinguishable e.*g. by flow cytometry" (Lindmo, page 188 bottom of col. 1, emphasis added). Clearly, neither the suggestion nor the expectation of success can be found in the prior art references.

D. THERE IS NO MOTIVATION IN THE PRIOR ART AS A WHOLE TO COMBINE THE TEACHINGS OF GRANGE *ET AL* AND LINDMO *ET AL.* IN A MANNER WHICH RENDERS THE CLAIMED SUBJECT MATTER OBVIOUS.

The Examiner has asserted that Lindmo teaches the use of different size particles, suggesting that one skilled in the art would be motivated to prepare these different sized particles in an agglutination assay reagent as taught by Grange with the expectation they would be useful in the same manner. In considering whether the subject matter Appellants claim would have been obvious to a person having ordinary skill in the art, the Examiner must first determine

what results the combined prior art teachings as a whole would have led ordinary persons having ordinary skill in the art reasonably to expect when using the compounds and methods Appellants claim. The expected results are then compared to the results Appellants report. See In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531-32 (Fed. Cir. 1988):

> [T]he full field of the invention must be considered; for the person of ordinary skill is charged with knowledge of the entire body of technological literature, including that which might lead away from the claimed invention. . . . Evidence that supports, rather than negates, patentability must be fairly considered.

As in the present invention, the particle size of Grange *et al* (300 nm diameter) is selected to enhance specific agglutination and falls in the same size range as that of the wavelength used for detection (220-600 nm). In Lindmo *et al*, the particle size (7-10 μm diameter) is selected to permit individual detection in the flow cytometer and is much larger than the size wavelength used for detection (550-590 nm). Appellants maintain that there is no reasonable expectation that the "relatively large" 7-10 μm diameter particles taught by Lindmo (See Lindmo page col. 2, lines 2-6) with antibody physically adsorbed to their surfaces (Lindmo, page 184, col. 2, lines 38-39) could be substituted for particles that are about 20-30 times smaller in diameter (300 nm diameter-See Grange page 367, line 12) with antibody covalently bound to their surfaces.

Most of the particles used in light scattering agglutination assays can be considered as colloidal in nature (See Applicants' Information Disclosure Statement: Newman *et al.*, Review Article, Ann. Clin. Biochem 1992, 22-42, page 29). Colloidal particles are within the size range of 1 nm to 1 μm "*excluding* those small single ions at one end *and particles that do not remain dispersed by Brownian motion at the other extreme*" (Id., emphasis added). On the other hand, individual particle counting requires particles that are in the range of 1 μm, significantly larger than particles used in agglutination assays (Id.). The literature surrounding the particle

counting technique suggests that it's use may be limited due to problems with the *particles themselves* rather than problems with the detection system since "there are a lot of difficulties with non-specific aggregation reactions" (Newman *et al*, page 26, col. 1). Lindmo's particles fall within this size range, that is, particles that do not remain dispersed by Brownian motion.

Newman *et al.* addresses the question of whether assays developed using nephelometric and turbidimetric detection systems can be made more sensitive by increasing their reaction times to those used for PCS and particle counting and states: "The evidence currently available suggests that this is unlikely, but, as has already been discussed, *direct comparison is often difficult because different particle sizes are appropriate for different detection systems...*" (Newman *et al.*, page 37 col. 1, emphasis added).

There are five basic characteristics of latex particles: size, refractive index, density, surface charge and number of surface reactive groups. (Newman *et al.* page 28, col. 1*)*. Newman *et al.* also describes the ideal theoretical particle for turbidimetric and nephelometric light scattering assays: "The size of the particle will depend on the instrumentation used but the size distribution must be narrow, preferably less than 5%. The particle should have a stable activated surface and the stability of the final reagent should be in excess of one year. *The 'ideal particle reagent' as discussed, also requires perfectly optimized diluent, something that is not as simple to describe as the particle itself*" (Newman *et al.*, page 37 col. 2, emphasis added).

Thus, one skilled in the art, aware of the vast number of factors affecting particle behavior would not find the observations of Lindmo *et al.* regarding the behavior of mondisperse particles in a flow cytometry assay to be predictive even of their ability to form the aggregates required by Grange and by the instant invention, much less what their behavior would be in such a hypothetical aggregated state.

Appellants arrived at the claimed invention as a whole through targeted research and development well beyond that which would be obvious to one of ordinary skill in view of the references cited. With unpredictability taught by the art, clearly there is no expectation of success provided by Brange *et al.* in view of Lindmo *et al.* Without such an expectation in the art, the disclosure that certain reagents exist which contain larger and smaller particles that have light scattering properties that can be distinguished in a flow cytometer makes it at best obvious to try. Patentability considerations based on an obvious to try logic are contrary to 35 USC 103 because that logic disregards consideration of the "invention as a whole" concept of 35 USC 103. In re Tomlinson, 363 F2d 928, 150 USPQ 623 (CCPA 1966 and In re Dien 371 F. 2d 866, 152 USPQ 550 (CCPA 1967).

Appellants submit that the Examiner did not "cast the mind back to the time the invention was made.... to occupy the mind of one skilled in the art who is presented only with the references, and who is normally guided by the then-accepted wisdom in the art." W.L. Gore Associates, Inc. v. Garlock, Inc. 721 F 2d 1540, 1553, 220 USPQ 303, 312 (Fed. Cir. 1983). If that is done, the invention set forth in the claims presented herein could only be held non-obvious to those skilled in the art at the time the invention was made. As established by Appellants herein, the cited references, whether taken alone or in combination, do not teach or suggest the combination.

E. THE EXAMINER HAS OFFERED NO PARTICULAR FACTUAL SHOWING REGARDING THE LOCUS OF THE SUGGESTION, TEACHING OR MOTIVATION TO COMBINE GRANGE *ET AL.* AND LINDMO *ET AL.*

The Examiner has offered no particular factual showing regarding the locus of the suggestion, teaching or motivation to combine Grange *et al.* and Lindmo *et al.* Mixing applications and materials does not elevate the disclosures into a teaching or suggestion to

combine Grange *et al.* and Lindmo *et al.* "The range of sources available ... does not diminish the requirement for actual evidence. That is, the showing must be clear and particular" *In re Dembiczak*, 50 U.S.P.Q. at 1617. The examiner states that it would have been obvious for one skilled in the art to combine the teachings of Grange *et al* with Lindmo *et al* "because Lindmo specifically taught that his binary microparticles ... can easily be incorporated with the concept of various mixtures of distinguishable microparticles coated with antibodies of different specificities in a simultaneous or homogenous assay of analytes *such as in the teachings of Grange* (emphasis added). In point of fact, the "incorporated" concept of various mixtures of distinguishable particles in a simultaneous assay taught by Lindmo *et al.* is directed to other *flow cytometry* assays for different antigens. What the reference actually teaches in that regard is that "one pair of particles could be used to provide a binary assay for each antigen *with the additional requirement that all particle types in the assay be individually distinguishable, e.g. by flow cytometry* " (Lindmo, page 188, col. 1, 3rd full paragraph, emphasis added, clearly teaching away from particles that agglutinate).

There is absolutely no teaching in Lindmo suggesting combination of their teachings with a simultaneous or homogenous agglutination assay of "such as taught in Grange" as the Examiner suggests. "Broad conclusory statements regarding the teaching of multiple references, standing alone, are not evidence." *In re Dembiczak*, 50 U.S.P.Q. at 1617. Case law calls for a "rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references." *Id. See also, C.R. Bard, Inc. v. M3 Sys., Inc.*, 48 U.S.P.Q. 2d 1225, 1232 (1998), (describing "teaching or suggestion or motivation [to combine]" as an "essential evidentiary component of an obviousness holding".) The Examiner's broad conclusion

regarding the teachings of the secondary reference is inadequate to support the obviousness rejection.

F. PRIMA FACIE CASE OF OBVIOUSNESS NOT ESTABLISHED

The Examiner bears the burden of establishing a prima facie case of obviousness based upon the prior art. (See *In re Fritch*, 23 USPQ 2d 1780, 1783 (Fed. Cir. 1992), *In re Oetiker*, 24 USPQ 2d 1443, 1446 (Fed. Cir. 1992), and *In re Deuel*, 34 USPQ 2d 1210, 1214 (Fed. Cir. 1995))

The court has held that

> The examiner bears the burden of establishing a prima facie case of obviousness. . . . Only if this burden is met does the burden of coming forward with rebuttal argument or evidence shift to the applicant. . . . When the references cited by the examiner fail to establish a prima facie case of obviousness, the rejection is improper and will be overturned. *In re Deuel*, 34 USPQ 2d 1210, 1214 (Fed. Cir. 1995)
>
> A prima facie case of obviousness is not established unless the relied-upon references contain some "teaching, suggestion, or incentive" supporting the combination. *In re Geiger*, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987).

It is respectfully submitted that there is no nexus in the record by which one of ordinary skill in the art would combine the teachings of Grange *et al* and Lindmo *et al* other than Appellants' disclosure. A prima facie case of obviousness has not been established.

II. 35 U.S.C. §112, SECOND PARAGRAPH ISSUES

In the Advisory Action of September 18, 2002, the examiner indicates that "the amendment of claim 1 raises new issues under 35 USC 112, second paragraph." A rejection under 35 U.S.C. §112, second paragraph, must be based upon the fact that one skilled in the art could not ascertain what is meant by the term "utilized in the claim." Please note In re Robins,

166 USPQ 552 at 556, where the CAFC held that such terms such as "aryl," and "substituted aryl radicals" are not indefinite under 35 U.S.C. §112, second paragraph, since one skilled in the art could ascertain what is encompassed within the meaning of this term. In the same way " capable of causing light scattering " and "at wavelengths suitable for the detection of agglutinated microparticle" define, respectively, a well known particle property and a well known wave length property which could be easily ascertained by one skilled in the art. In this regard, please note page 8, lines 3-9, of the instant application, which specifically sets forth that the size and/or the refractive index ratio of the microparticles is such that they can cause light scattering at the wavelength used for detection of agglutinated microparticles. That detection wavelength is usually from 300 nm to 1200 nm. Accordingly, particle size is generally chosen to be substantially smaller or slightly smaller than that wavelength. The mean diameter of microparticles is suitably from 30 to 600 nm, preferably from 50 to 500 nm. Applicants concede that "said microparticles lacks clear antecedent basis and propose amending the claim to recite " said first and second microparticles."

CONCLUSION

Appellants respectfully submit that there is no teaching, suggestion or motivation for combining the teachings of Grange *et al.* with the teachings of Lindmo *et al.* A prima facie case of obviousness has not been established. Appellant therefore respectfully requests that the Board reverse the Examiner as to the issue of whether Appellants' claimed invention is unpatentable over Grange *et al.* in view of Lindmo *et al.* under 37 C.F.R. §103(a). Since the remainder of the rejections under 37 C.F.R. §103(a) require the combination of Grange *et al* Lindmo *et al.*, they will be obviated by the withdrawal of the rejections based on these two references only.

Applicants further submit that the amended claims (with the minor additional amendment proposed above) meet the requirements of 35 U.S.C. 112, second paragraph.

Respectfully submitted,

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APPENDIX A

CLAIMS:

1. A reagent for performing an agglutination assay for determining the amount of an analyte in a sample, said reagent comprising a mixture of microparticles, said mixture comprising first microparticles having a mean diameter and a refractive index, wherein said first microparticles are selected from the group consisting of inorganic, organic and polymer materials suitable for microparticle enhanced light scattering assays and are coated with a first binding partner for said analyte, and second microparticles having a mean diameter and a refractive index, wherein said second microparticles are selected from the group consisting of inorganic, organic and polymer materials suitable for microparticle enhanced light scattering assays and are coated with a second binding partner for said analyte, said first microparticles having stronger light scattering properties than said second microparticles, and said first binding partner coated upon said first microparticles having a higher reactivity for said analyte than said second binding partner coated upon said second microparticles, said microparticles being capable of causing light scattering at wavelengths suitable for the detection of agglutinated microparticles.

2. The reagent of claim 1, wherein said mean diameter of said first microparticles is greater than said mean diameter of said second microparticles.

3. The reagent of claim 2, wherein said refractive index of said first microparticles is greater than said refractive index of said second microparticles.

4. The reagent of claim 3, wherein a ratio of the mean diameter of said first microparticles to the mean diameter of said second microparticles ranges from about 1.5 to about 4.0.

5. The reagent of claim 4, wherein the ratio of the mean diameter of said first microparticles to the mean diameter of said second microparticles ranges from about 1.7 to about 3.2.

6. The reagent of claim 3, wherein a ratio of the concentration of said first microparticles and the concentration of said second microparticles in said mixture ranges from about 0.01 to about 5.0.

7. The reagent of claim 6, wherein a ratio of the concentration of said first microparticles and the concentration of said second microparticles in said mixture ranges from about 0.05 to about 2.0.

8. The reagent of claim 1, wherein a ratio of the detection limits of an assay performed with said first microparticles and the detection limits of an assay performed with said second microparticles ranges from about 0.01 to about 5.0.

9. The reagent of claim 1, wherein said analyte is a nucleic acid and said first and second binding partners are oligonucleotide capture probes.

10. The reagent of claim 1, wherein said analyte is antigenic and said first and second binding partners are immunological binding partners.

11. The reagent of claim 10, wherein a ratio of the dissociation constants of said first and second binding partners for said first and second microparticles is from about 0.01 to about 5.

12. The reagent of claim 10, wherein said first and second binding partners are monoclonal antibodies or fragments thereof.

13. The reagent of claim 12, wherein said analyte comprises non-repetitive epitopes, said first microparticles are coated with at least two sets of first binding partners reactive for

different epitopes on said analyte, and said second microparticles are coated with at least two sets of second binding partners reactive for different epitopes on said analyte.

14. The reagent of claim 12, wherein said analyte comprises non-repetitive epitopes, and said first microparticles comprise a first portion and a second portion, wherein said first portion is coated with a first binding partner portion reactive with said analyte and said second portion is coated with a second binding partner portion reactive with said analyte; and said second microparticles comprise a first portion and a second portion, wherein said first portion is coated with a third binding partner portion reactive with said analyte and said second portion is coated with a fourth binding partner portion reactive with said analyte, wherein said third and fourth binding partner portions coated upon said second microparticles have lower reactivities for said analyte than said first and second binding partner portions coated upon said first microparticles, and said first, second, third, and fourth binding partner portions are directed to different epitopes of said analyte respectively.

15. The reagent of claim 13, wherein the mean diameter of said first microparticles is greater than the mean diameter of said second microparticles.

16. The reagent of claim 15, wherein the refractive index of said first microparticles is greater than the refractive index of said second microparticles.

17. The reagent of claim 14, wherein the mean diameter of said first microparticles is greater than the mean diameter of said second microparticles.

18. Canceled

19. Canceled

20. The reagent of claim 1, wherein the composition of said first and second microparticles is selected from the group consisting of selenium, carbon, gold, a nitride of carbon, a nitride of silicium, a nitride of germanium, an oxide of iron, an oxide of titanium, an oxide of silicium, an epoxy resin, polyvinyl chloride, polyvinylidene chloride, polyalpha-naphthylmethacrylate, polvinylnaphthalene, polystyrene and a copolymer thereof.

21. Canceled